FIRST

Florida Eye Research & Surgical Therapy Institute

Ocular Immunology Brochure

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1. ROLE OF IMMUNOLOGY

Immunity
A state of resistance to an agent, the pathogen that normally produces an infection. Pathogens include microorganisms such as bacteria and viruses, as well as larger parasites. The immune response that generates immunity is also responsible in some situations for allergies, delayed hypersensitivity states, autoimmune disease, and transplant rejection.

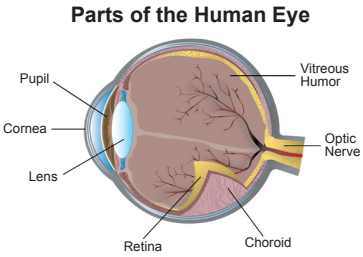
Immunology
The division of biological science concerned with the native or acquired response of complex living organisms to the intrusion of other organisms or foreign substances. Immunology is the study of all aspects of the immune system including its structure and function, disorders of the immune system, blood banking, and immunization and organ transplantation.

2. OCULAR INFLAMMATORY DISEASE

Ocular Inflammatory Disease (OID) is a general term for inflammation affecting any part of the eye or surrounding tissue. Inflammation involving the eye can range from the familiarallergic conjunctivitisof hay fever to rare, potentially blinding conditions such as uveitis, scleritis, optic neuritis, keratitis, orbital pseudo tumor, retinal vasculitis, and chronic conjunctivitis. Broadly speaking, if inflammation develops in the eye(s), or in the optic nerve, blood vessels, muscles or other tissues that surround the eye, the resulting illness is classified as an ocular inflammatory disease (or OID for short).

3. ANATOMY OF THE EYE

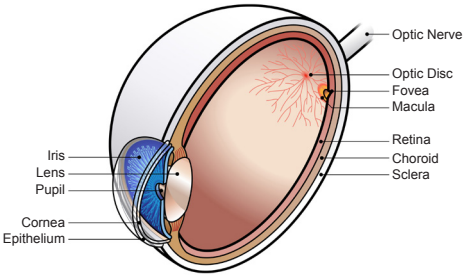
The location of the inflammation governs the diagnostic name for the ocular inflammatory disease. For example, uveitis is inflammation in the uveal tract; scleritis is inflammation of the sclera, pars planitis is inflammation of the pars plana, and so forth.



UVEA

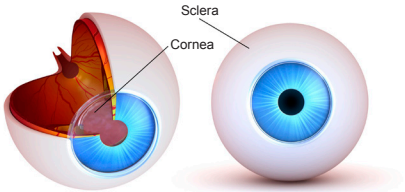
The middle layer of the eye is called the uvea or uveal tract. It is made up of the iris, the ciliary body, and the choroid. The uvea surrounds the eye like a tunic (coat). The visible part of the uvea, in the front, is the iris. Inflammation in any of the parts of the uveal tract is called uveitis. Inflammation inside the eye is a medical emergency because, untreated, it will lead to vision loss.

Cornea



The cornea is a transparent, dome-shaped window covering the front of the eye. It is a powerful refracting surface providing 2/3 of the eye's focusing power. Like the crystal on a watch, it gives us a clear window to look through. Because there are no blood vessels in the cornea, it is normally clear and has a shiny surface. The cornea is extremely sensitive; there are more nerve endings in the cornea than anywhere else in the body. Inflammation in the cornea is called Keratitis. Chronic or severe keratitis can cause corneal opacity, ulceration or corneal perforation, and consequently vision loss.

Sclera



The sclera is commonly known as "the white of the eye". It is the tough opaque tissue that serves as the eye's protective outer coat. The inflammation of the sclera is called Scleritis. The inflammation characteristically has the capacity to spread to other ocular tissues of the anterior segment and/or posterior segment. Consequently, if you do not begin treatment immediately, the condition poses the risk of severe visual loss in the form of cataracts, secondary glaucoma, choroidal or exudative detachment or optic atrophy.

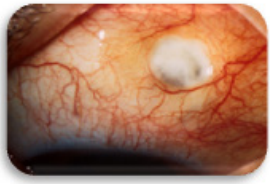
4. UVEITIS AND OCULAR IMMUNOLOGY

Uveitis diseases are often chronic and if untreated can be sight-threatening. In a large population-based study uveitis has recently been reported to have an incidence of 52.4 / 100.000 person - year and a prevalence of 115.3/100.000 persons. In the USA, inflammatory uveitis is estimated to account for about 10% of severe visual handicaps; thus, this group of diseases is neither rare nor trivial.

Uveitis refers to inflammation of one or all portions of the uveal tract (iris, ciliarybody, and choroid). It can be caused by any number of conditions, from an autoimmune disorder to an infection or a complication of surgery. Symptoms range from pain, photophobia, and blurred vision in anterior uveitis, to floaters and blurred vision in intermediate uveitis, and loss of visual field or decreased vision in posterior uveitis. Depending on the type and severity of the condition, treatment may include corticosteroids, NSAIDs[1], immunomodulatory therapy, or surgery.

[1]Non-steroidal Anti-Inflammatory Therapy and RecurrentAnterior Uveitis.Vanessa Fiorelli, MD et al. OculImmunolInflamm. 2010 Apr;18(2):116-20.

5. SCLERITIS AND OCULAR IMMUNOLOGY



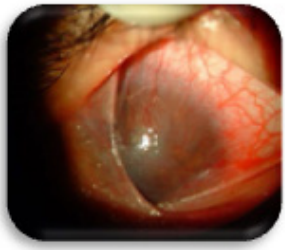
Scleritis is a severe inflammatory condition and without treatment, may become progressively destructive, leading to vision loss of the eye. Scleritis is often associated with systemic disease. Among the most common related disorders are rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, polyarteritisnodosa, Wegener's granulomatosis, herpes virus, gout and syphilis.

Corticosteroid eye drops help reduce the inflammation. Sometimes corticosteroids pills are taken by mouth. Newer, non-steroid anti-inflammatory drugs (NSAIDs) may be used in som cases. Recent articles revealed that NSAIDs can decrease the relapses in selected patients, but also showed that patients with serious systemic conditions may not respond to NSAIDs, and may require immunotherapy (IMT)[2].

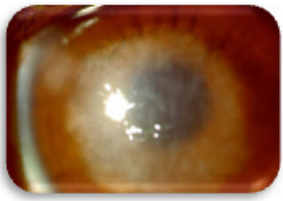
[2]Non-steroidal Anti-Inflammatory Therapy and Immunotherapy in Anterior Scleritis - Vanessa Fiorelli, MD et al, Ocular Immunology, ARVO 2009.

6. KERATITIS, KERATOCONJUNCTIVITIS, and OCULAR IMMUNOLOGY

Keratitis refers to cornea inflammation, and Keratoconjunctivis refers to inflammationof the eye involving both: the corneaand conjunctiva.



Keratoconjunctivitis can be due to diverse causes, including infectious and/or autoimmunity. Autoimmune keratoconjunctivits most commonly occurs in patients with collagen vascular diseases, among them, ocular cicatrizing pemphigoid, Stevens-Johnson syndrome, atopic keratoconjunctivis, trachoma, rosacea, and ocular burn. The course of some of these diseases is characterized by chronic inflammation with relapsing and progressive conjunctival fibrosis. The results are severe corneal epitheliopathy, corneal ulceration, secondary infection, corneal vascularization, and may subsequently cause blindness.



In these patients with chronic cicatrizing conjunctivitis, systemic treatment with immunomodulatory therapy is necessary to control allogenic reaction and prevent further ocular surface inflammation[3].

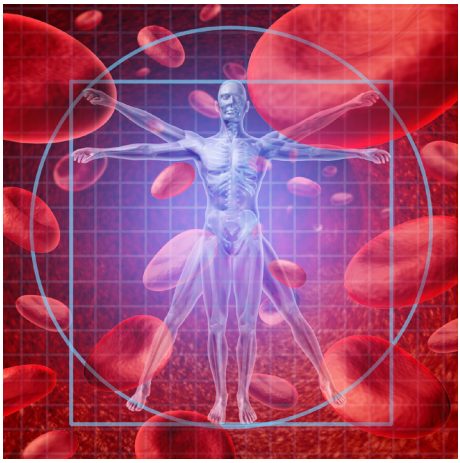
Conventional management begins with adjuvant therapies such as artificial lubrication, topical and systemic corticotherapy and in severe cases immunomodulatory therapy (dapsone, azathioprine, cyclophosphamide, cyclosporine and systemic immunoglobulin). Occasionally, the conventional immunomodulatory therapy applied is inefficient in the control of ocular inflammation. Moreover, systemic side effects and toxicity are responsible for the discontinuity of the treatment.

[3] Systemic Monoclonal Antibody Therapy (Daclizumab) in the Treatment of Ocular Cicatrizing Disease Refractory to Conventional Therapy. Vanessa Fiorelli, MD; Allen Jackson, MD, et al. Curr Eye Res. 2010 Dec;35(12):1057-62. Epub 2010 Oct 7.

7. THE IMMUNE SYSTEM

Inflammation

Literally speaking, inflammation means setting on fire. Inflammation results from the body 's attempt to eliminate a foreign body or germ and helps to prevent further injury. Inflammation takes place to activate immune mechanisms and to eliminate thoroughly the source of infection. Antibodies are proteins in the family of immunoglobulins, and antigens are anything that the immune system recognizes as non-self or foreign and, therefore, trigger an immune response.



Inflammation is a complex process involving many different kinds of white blood cells: granulocytes (neutrophils, basophile, and eosinophils) and some immune specific white blood cells called B and T lymphocytes along with their antibodies and cytokines. In all inflammatory diseases there is the migration of these specific types of white blood cells out of the bloodstream into surrounding tissues. A variety of cells are activated, including mast cells and macrophages. Inflammation results in local attraction of immune cells, increased blood supply, and increased vascular permeability.

These cells release agents (chemicals), such as cytokines, to boost immune responses and kill invading bacteria, viruses, and parasites or anything that the immune system perceives as foreign (antigen), or non-self. Part of their response is bringing antibodies to the site; the antibodies then attach to antigens and mark them for death.The linking of the antibody to the antigen forms an immune complex. Immune complexes circulate through the blood. Usually they are removed quickly, but occasionally they are lodged into tissues and cause inflammation.

Inflammation can develop in any part of the body, including the eyes and their surrounding structures. Normal healthy tissue can be injured by inflammation during this process (innocent bystander injury). Inflammation is marked by four signs: swelling, redness, heat, and pain. When this happens in or around the eyes, the affected region (the eyelids, the sclera, the iris, the uvea, the retina, the optic nerve) becomes red, sore, and swollen.

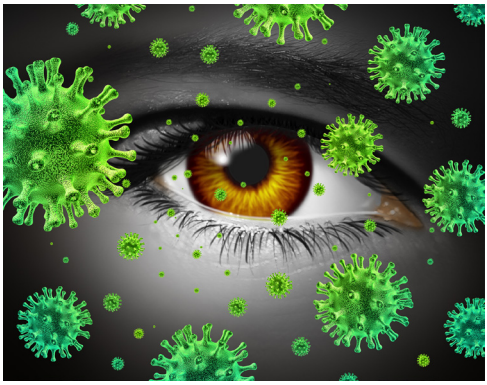
If eye inflammation is long lasting (chronic) or severe, damage to delicate tissues and blood vessels in and around the eye can occur, resulting in vision loss.

Autoimmunity
The immune system is designed to protect and defend the body from foreign intruders (germs). The immune system is complex. Essentially, it contains several different types of cells, some of which function like security guards, which are constantly on patrol looking for any foreign invaders. When they spot one, they take action and eliminate the intruder.

Autoimmune diseases are characterized by the body's immune responses being directed against its own tissues, causing prolonged inflammation and subsequent tissue destruction. A number of autoimmune diseases exist, the most familiar of which is rheumatoid arthritis. In rheumatoid arthritis, the dysregulated immune system attacks the joints.This dysregulation of the immune system is termed autoimmunity, or immune attack against self. The reason why this happens is unknown. The result of autoimmunity is chronic inflammation.

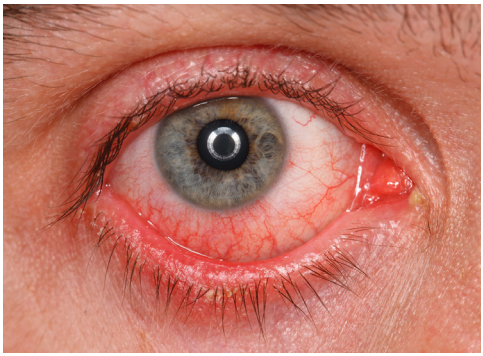
Autoimmune-mediated Ocular Inflammatory Disease
In some forms of ocular inflammatory disease, like any other systemic autoimmune disease, the immune system loses its ability to tell the difference between a foreign intruder and a person's own normal tissues and cells. So, in essence, the guarding cells lose their memory, and they mistakenly identify the person's own normal cells as foreign (antigens) and, subsequently, take action to eliminate them.

A number of autoimmune diseases exist in which the eye or various parts of the eye may be attacked. In ocular inflammatory disease, often the autoimmune disease is systemic, not only involving the eye but a variety of organs throughout the body. The most common examples of such diseases include rheumatoid arthritis, systemic lupus erythematosus, polyarteritisnodosa, relapsing polychondritis, Wegener's granulomatosis, scleroderma, Behcet's disease, inflammatory bowel disease (Crohn's), Stevens-Johnson syndrome, and rosacea.However, the eye may in certain instances be the specific and only target affected by certain autoimmune diseases. Some such diseases include ocular cicatricialpemphigoid, Mooren's corneal ulcer, and some forms of uveitis, including Birdshot retinochoroidopathy, Vogt-Koyanagi-Harada syndrome, and sympathetic ophthalmia.



8. CAUSES OF OCULAR INFLAMMATORY DISEASE

The forms of ocular inflammatory diseases that are most commonly seen include ocular allergy, cicatricialpemphigoid, scleritis, peripheral ulcerative keratitis, retinal vasculitis, chronic conjunctivitis, along with anterior, intermediate, and posterior uveitis. They can be infectious or noninfectious, traumatic, drug-induced, or malignant.



There are several reasons why the conjunctiva can become inflamed. When it gets irritated or infected it becomes red, which is medically known as conjunctivitis, also called “pink eye”. This describes a group of diseases that cause swelling, itching, burning, and redness of the conjunctiva. Conjunctivitis can be caused by a bacterial or viral infection, allergy, environmental irritants, contact lens products, eye drops, or eye ointments.

The eye is constantly exposed to a variety of pathogens, but infections occur when the normal defenses of the eye are compromised. The source of the infection may be local (e.g., from the eyelids) or remote (e.g., from the sinuses) and can be the result of trauma, eye surgery, contact lens wear, immune deficiencies, or other diseases resulting in bacteria growth or viruses.

There are several causes of noninfectious OID (Ocular Inflammatory Disease), one of which is autoimmune disease. In many cases, the autoimmune disease is systemic (affecting the body) and also produce inflammation in specific parts of the eye. The OID will then be identified according to that part of the eye, which has inflammation. For example, juvenile rheumatoid (or idiopathic arthritis) is associated with inflammation in the anterior part of the eye, known as anterior uveitis or iritis. The area of inflammation in the eye is helpful to the doctor in the development of differential diagnoses to detect the cause of OID.

Autoimmune diseases can also affect the eye alone; such as in the following ocular diseases: Birdshot retinochoroidopathy, Fuchs’ heterochromiciridocyclitis, Vogt-Koyanagi-Harada, ocular cicatricialpemphigoid. The other cause of noninfectious OID is termed idiopathic. Idiopathic OID is basicallya diagnosis of exclusion. That is, no infection or associated systemic illness can be identified at the time of the diagnosis of eye inflammation. In this instance, inflammation is located entirely in the eye or its structures.

This form of OID does not tend to have blood tests that can be used to follow the disease course. The inflammation is evaluated by the doctor using the slit lamp.

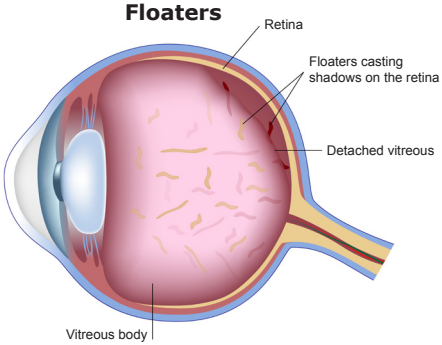
Drug or medication can also be the cause of ocular inflammatory disease. Some drug examples arecidofovir, rifabutin, and sulfonamides or topical corticosteroids and latanoprost. Vaccines and even skin tattoos can be inducers of OID. Certain cancers can cause OID, such as lymphoma, lung cancer, and breast cancer.

9. SIGNS AND SYMPTOMS OF OCULAR INFLAMMATORY DISEASE

Inflammation can affect any part of the eye or its surrounding structures. The symptoms of inflammation for the most part depend on the area in the eye of the inflammation. Most common signs and symptoms are:

Pain and Redness

Floaters

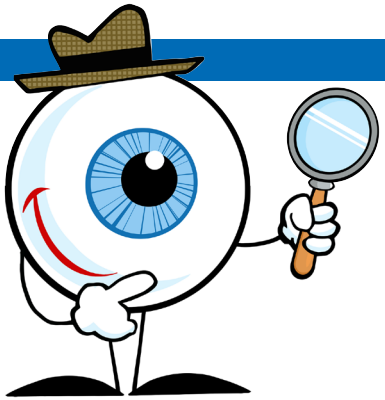


Decreased vision

Light sensitivity

Eye pain, severe light sensitivity, and any change in vision are considered emergency signs and need immediate attention by an ophthalmologist

10. GETTING A DIAGNOSIS



When a patient presents with ocular inflammation, the diagnostic workup begins with the signs and symptoms. Each facet of the history and physical examination serves to either increase or decrease the probability of a target disorder being present. Usually, when an eye problem is suspected, a patient is first sent to a general, comprehensive ophthalmologist. He or she will perform a thorough eye exam, including:

- Tests of visual acuity, to determine if vision has decreased.
- Eye pressure: Measures of the pressure inside the eye to make sure it has not reached levels that might be dangerous. This painless test can be done on the slit lamp by a tonometer, or without a slit lamp using a tonopen. These measure the pressure inside the eye by lightly pressing on the surface of the eye.
- A slit lamp exam, in which a narrow beam of light is shone into the eye so that a magnifying lens can closely examine the highlighted portion of the eye.
- A fundoscopic exam, in which the pupil is dilated (widened) so that the ophthalmologist can look into the eye and see structures in the back of the eye.

In addition, the physician probably will ask about the medical history, and may order blood tests, and image tests. Because uveitis or external ocular disease is often associated with a viral infection or an autoimmune disease, other conditions need to be discovered and treated as well.
Specific immune diseases can cause ocular inflammatory disease. Sometimesdiagnosis may require a referral to a specialist (an Ocular Immunologist) for further diagnostic evaluation and treatment.
The ocular immunologist will review the following, along with his or her exam, to help make the diagnosis:

- The individual's entire medical history;
- An analysis of the results obtained in routine laboratory tests and/or imaging; many times a repeat in serologic testing is needed;
- Specialized imaging of the eye and its structures, and
- Some specialized blood tests related to the immune system.

11. NON-INFECTIOUS INFLAMMATORY DISEASE TREATMENT

The treatment of ocular non-infectious inflammatory disease,is aimed at eliminating inflammation. This in return will alleviate pain, stop formation of new floaters, and normalize any acute changes in vision. It is crucial to stop the inflammation before delicate tissues in the eye are damaged in order to prevent secondary complications and permanent vision loss. The goal of treatment is prevention of recurrence without chronic use of steroids. The long-term goal is total remission of the OID, off of all medication. The road to remission can be bumpy as some forms of OID can be very aggressive and "stubborn" to control.

Regardless of the form of autoimmunity, any autoimmune disease affecting the eye will require systemic (e.g., oral as opposed to local, topical, ocular) therapy. The components of the immune system are systemic (residing outside of the eye) and therefore, regulation of those components will require systemic therapy. For non-infectious causes of inflammation,the object of the stepladder approach is to modify the immune system in order to stop it from inappropriately attacking the eye and causing inflammation.

The Stepladder Approach

The first step is steroid medication. A steroid is an anti-inflammatory immunosuppressive medication that can be administered in many forms: topical drops, oral, injection, or intravenous infusion. The form of steroid that is prescribed depends on the severity and type of OID one has. Steroid is an effective medication in quickly aborting acute inflammation, but used long-term it results in its own set of complications such as stomach ulcer, osteoporosis, diabetes, cataract, glaucoma, cardiovascular disease, weight gain, fluid retention, and Cushing's syndrome.

If inflammation continues to recur after weaning off of steroids, the doctor will move to the next step, non-steroidal anti-inflammatory drugs (NSAIDs). Some examples of NSAIDs include Diflunisal, Celebrex, or Naprosyn. NSAIDs are a non-steroidal type of medication aimed at suppressing inflammation. Oral NSAIDs require monitoring of the liver and kidney function. Certain types of oral NSAIDs, if used long-term, will need added medication for protection against stomach ulcers. Some studies revealed control of the relapses with oral NSAIDs, for selective diseases.

In addition, eye drops that dilate the pupil may be prescribed, if inflammation is in the iris, to prevent spasm of the muscles of the iris and ciliary body that cause pain. The doctor may recommend sunglasses because bright light may cause discomfort. Additional treatment may also be required for complications of OID, such as glaucoma and macular edema.

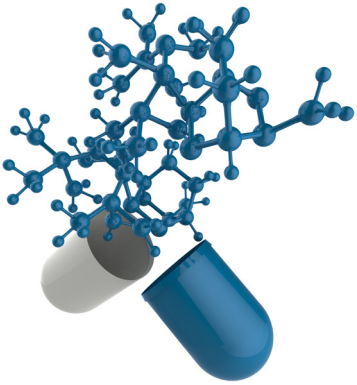
Immunomodulatory Therapy
When inflammation persists despite the use of NSAIDs, the next approach is immunosuppressive chemotherapy medications or immunomodulatory therapy (IMT). Such medications include Methotrexate, CellCept, Imuran, Cytoxan, Leukeran and Cyclosporin.

The treatment will start with the type of medication that the doctor believes is most appropriate for a particular type of OID. In addition, the medication that has the least potential for side effects is favored.

The use of such medication requires special, regular monitoring (blood tests) in order to ensure that no hidden side effects are creeping in. Regrettably, many people (including a surprising number of physicians) are unaware of the very favorable risk-to-benefit ratio of such medications used in the doses that rheumatologists, ocular immunologists, and other specialists prescribe for immunomodulation of autoimmune disease. As a result, many people equate the use of such medicine with the high doses given in cancer chemotherapy, with all the risks and side effects that occur at these high doses.

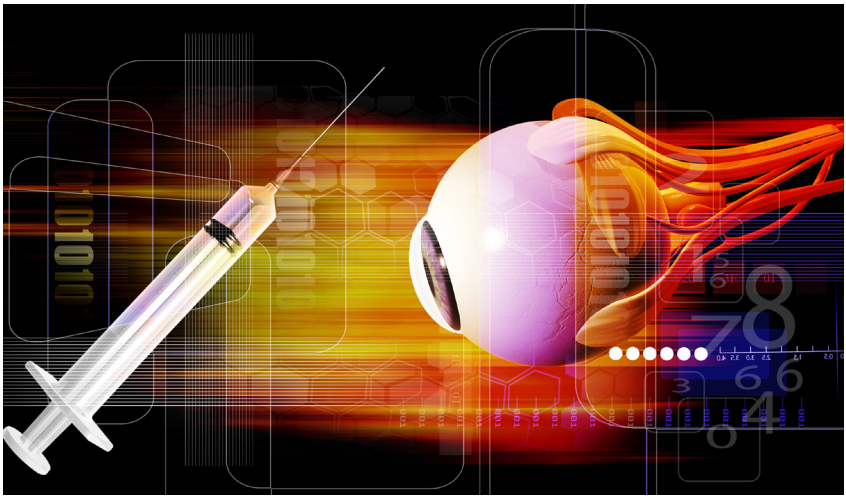
This is not at all what IMT for OID is all about. Used correctly by a physician who is an expert in such matters, the patient with OID who is treated with IMT should look and feel normal. If an IMT medication disagrees with a patient, that medication should be stopped and another tried, so that the goal of no inflammation on no corticosteroids and no significant IMT side effects is achieved.

Biologic Medications
The newest entries into the therapeutic arena are medications that target specific mediators of the immune response. These medications employed for the treatment of autoimmune diseases are called biologic response modifiers (BRM) or biologics. The biologics more specifically target certain elements of the immune system, and in so doing, avoid some of the potential risks of the more conventional IMT medications. Such medications include Humira, Remicade, Zenapax, Rituximab, Benlysta, Enbrel and Immunoglobulin (IgG).



A BRM medication may be added to a conventional IMT medication in the stepladder approach in aggressiveness of therapy for stubborn inflammation. It has been shown that two TNF-alpha antagonists (Humira&Remicade), and the antagonist of interleukin-2 receptors (Zenapax) has been found to effectively modulate the immune response in patients with uveitis, and selected cases of chronic keratoconjunctivitis. Another biologic (Enbrel) however,was concluded to be ineffective in modifying recurrences of uveitis.

Intraocular pharmacotherapy



Another new treatment modality is the use of intraocular pharmacotherapy via intraocular (intravitreal) injection and surgically placed implants. Several reports have confirmed the treatment benefit of intravitreal triamcinolone (usually 4 mg in 0.1cc) for the management of refractory cistoid macular edema (CME) frequently secondary to intraocular chronic inflammation. Unfortunately, the intravitreal half-life of triamcinolone is relatively short, and multiple injections may be necessary. Cataract formation and elevated IOP are common, and the risk of endophthalmitis(usually sterile) is approximately 0.1%.

Reports are emerging regarding the off-label use of the full-length humanized anti-VEGF monoclonal antibody bevacizumab in the treatment of refractory CME and neovascular complications of uveitis. However, as with triamcinolone, serial injections may be necessary, and the long-term tolerability and safety of this medication is unknown.

A sustained-release fluocinolone implant (Retisert) was recently FDA approved for the treatment of refractory noninfectious uveitis.
The drug is released for 30 months and effectively controlled inflammation in nearly all eyes in the phase 3 study, allowing for the tapering of systemic steroids and immunomodulatory agents. Cataract formation is a near certainty in phakic eyes, and the risk of glaucoma is nearly 60%.
Careful patient selection is a must.

"Off-Label Use" of Medications

It should be noted here that none of the medications mentioned in this pamphlet, including IMT and BRM (biologic response modifiers) medications, are approved for treating OID by the United States Food and Drug Administration (FDA). That is to say the pharmaceutical companies who manufacture these medications have never conducted the randomized clinical trials required by the FDA in order for the companies to include treatment of OID in the package insert or "label" for the medication. Therefore, doctors who employ such medications for treating OID do so "off-label." Off-label use is perfectly legal and appropriate, if in the doctor's opinion, it is in the patient's best interest to proceed with such treatment. One can find in the medical literature many clinical reports in the success of the use of these types of medications mentioned above.

Durations of treatment

The duration of treatment varies from person to person and depends on the type and cause of ocular inflammatory disease. Simple forms of uveitis, for example, may respond to treatment within days and may not recur. Chronic (long-term, recurring) forms of ocular inflammatory disease that threaten vision can be very difficult to cure and require persistence on the part of the treating physician(s) and patient. The same happens in patients with scleritis, and chronic external disease that continue with relapses despite the initial treatment. The length of time required to get the disease into a durable remission on IMT is difficult to quantify and is very individualistic, but a minimum of two years is a reasonable estimate. During treatment on IMT, one can expect visits to the ophthalmologist every 4-6 weeks approximately. With appropriate, targeted treatment, most people with ocular inflammatory disease will become well controlled and progress to remission. Once in remission from ocular inflammatory disease, you should expect to have regular follow-up visits to your doctor to make sure that the disease remains in remission.

What kind of doctor treat?
It may be apparent after reading this material that doctors who treat ocular inflammatory disease must have special training in both ophthalmology and in ocular immunology. This type of specialty training is accomplished at an advanced level and is termed Fellowship training. Doctors with this training are specialists in the immunology of the eye, as well as comprehensive ophthalmology. Ocular immunologists, because of their specialty training, are better able to hunt for the cause of your ocular inflammatory disease. Such specialists apply the principles of diagnosis of ocular inflammatory disorders in order to initiate appropriate, disease-directed evaluations. It is the cause of the OID, whether idiopathic or not, that directs treatment.

The training of the ocular immunologist also provides him or her with knowledge and experience in the use of the stepladder approach to care. The ocular immunologist is also experienced in knowing when one needs to switch from one IMT to another, how to prevent any potential side effects through close monitoring, and manage side effects if they occur. Furthermore, Ocular Immunologists have special skills with regard to the surgical management of ocular inflammatory disorders.

FREQUENTLY ASKED QUESTIONS

• How did I get uveitis? Did I catch it from someone?
Approximately 60 different things – infectious, non-infectious, as well as malignant etiologies – can cause uveitis. If the cause of uveitis is infectious, it is possible that you "caught"that infectious agent from somebody, some thing, or some animal, including your household pets. If the uveitis is on the basis of autoimmunity (the most common form of uveitis), then the uveitis is the manifestation of ones own immune system inappropriately "attacking" part of its own body. In such cases, one does not "catch" it.

• Can uveitis and chronic ocular external disease be treated?
Physicians must be able to identify the underlying cause to most effectively start the appropriate treatment. "The proper treatment for one cause would in many instances be deleterious in the care of patients with chronic ocular inflammatory disease from another cause. Regardless of the form of autoimmunity, any autoimmune disease affecting the eye will require systemic(e.g., oral as opposed to local, topical, ocular) therapy. The components of immune system reside outside of the eye itself in the body systems and therefore called systemic. Regulation of those components will therefore require systemic therapy.

• Does stress trigger OID?
We do not know for certain. There are many anecdotal reports (personal accounts) of patient's eye inflammation flaring-up during or after a stressful time, but this question requires further scientific study. Stress does not cause the illness itself, but stress is known to modify how the immune system functions. This has implications for stirring up all inflammatory illnesses, including ocular inflammatory disease.

• What is the difference between CELLS and FLARE?
Cells: The term "cells", as used to in ophthalmology, generally refers to a collection of white blood cells (leukocytes) in the anterior chamber of the eye. Cells can be observed on slit lamp examination floating in the fluid in the front of the eye. The amount of white blood cells is the measure of uveitis activity, and is scaled from 1 to 4, depending on the severity, (minimal - 1 being the least severe inflammation and 4 being the most severe inflammation).
Inflammatory cells can also accumulate in the vitreous. This occurs as a result of inflammation in intraocular structures such as the ciliary body, retina, and choroid. Cells in the vitreous can be living or dead, and both can become immutably affixed to vitreous fibers.
Flare: Flare is protein in the anterior chamber caused by leakage from inflamed blood vessels in the iris. It is not always a measure of inflammation. Flare is measured on a scale from 1 to 4, with 4 being the most severe. Flare becomes chronic after inflammation has produced permanent changes to blood vessels, and so "flare" may be present even when the patient is not having a "flare-up" of inflammation. Flare in the vitreous can also be observed and rated.

• Are flare-ups related to hormones?
Some women notice each time their inflammation flares up, that the episode invariably occurs at the same point in their menstrual cycle, suggesting that certain hormone level changes can be associated with flare-ups. It has been noted that OID improves for many during pregnancy. Some authors postulated that the rapid withdrawal of the anti-inflammatory effects of estrogen and/or progesterone in the late luteal phase may explain the increase in inflammatory attacks during the late menstrual cycle.

• What is the explanation for FLOATERS?
Floaters appear as gray or black specks, strands, or "cobwebs" in front of the eyes. As the eyes move, the floaters move too. Floaters are caused by particles, such as white blood cells and vitreous condensates, suspended in the vitreous gel, which is the clear jelly-like fluid that fills the posterior portion of the inside of the eye. The floaters cast shadows on the light sensitive retina, and it is actually the shadow of the floaters that is seen.

Eye (vitreous) floaters is from thelatin-derived term muscaevolitantes (meaning " flying files"), or from the French-derived termmouchesvolantesmeaning are little "cobwebs" or specks that float about in your field of vision. They are small, dark, shadowy shapes that can look like spots, thread-like strands, or squiggly lines. They move as your eyes move and seem to dart away

• Besides the arthritic condition, are there other risk factors for uveitis? How should rheumatologists recognize and manage them?
The reality is that uveitis can occur as part of the underlying autoimmune disease, and if we look at all patients with uveitis, approximately 50% will have an underlying systemic disease, whereas in the other 50% there is likely no systemic disease that can be identified. We classify the latter group of patients as presenting with idiopathic uveitis. From the clinical perspective, other potential risk factors that are perhaps tangentially related to the uveitis, from a clinical perspective, as mentioned for juvenile idiophathic arthritis, the patterns of disease is very important in defining risk. Other potential risk factors are not well delineated, although HLAB27 positivity, for example, has been found to be more common in people who have uveitis in general, irrespective of whether they have rheumatic disease.

• How are autoimmune eye disease treated in the FERST Eye Institute?
We employ a "stepladder" approach to the care of our patients with ocular autoimmune disease, generally beginning with steroid drops, advancing to steroid injections and/or pills, adding an oral, non-steroidal anti-inflammatory medication, culminating in the use of an immunomodulatory, chemotherapeutic drug if the patient's ocular inflammation continues or continues to recur each time the steroid medicationsare tapered and stopped.

MEDICATIONS USED IN OCULAR INFLAMMATORY DISEASE

1. Drug Category: Cycloplegics

Symptoms and complications of inflammation can be tempered with topical cycloplegic agents. Both short-acting drops (e.g., cyclopentolate) and long-acting drops (e.g., atropine) can be used to decrease photophobia caused by ciliary spasm and to break-up or prevent the formation of posterior synechiae.

Drug Name	*CYCLOPENTOLATE (I-PENTOLATE, CYCLOGYL, AK-PENTOLATE)*
Description	Prevents muscle of ciliary body and sphincter muscle of iris from responding to cholinergic stimulation. Induces mydriasis in 30-60 min, and cycloplegia in 25-75 min. Effects last up to 24 hours.
Adult Dose	1 gtt OU qd/qid.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity; narrow-angle glaucoma.
Interactions	Decreases effects of carbachol and cholinesterase inhibitors.
Pregnancy	C- Fetal risk revealed in studies in animals, but not established or not studied in humans; may use if benefits outweigh risk to fetus.
Precautions	Caution in patients (e.g., elderly) where increased IOP may be present; may cause toxic anticholinergic adverse effects (common in children, especially infants), but incidence rare when used sparingly; compressing lacrimal sac by digital pressure for 1-3 min following application may minimize systemic absorption.

Drug Name	*ATROPINE (ISOPTO)*
Description	Acts at parasympathetic sites in smooth muscle to block response of sphincter muscle of iris and muscle ofciliary body to acetylcholine, causing mydriasis and cycloplegia.
Adult Dose	1 gtt OU qid/bid.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity; thyrotoxicosis; narrow-angle glaucoma; tachycardia.
Interactions	Coadministration with other anticholinergic has additive affects; pharmacologic effects of atenolol and digoxin may increase with atropine; antipsychotic effects of phenothiazine's may decrease with this medication; tricyclic antidepressants with anticholinergic activity may increase effects of atropine.
Pregnancy	C-Fetal risk revealed in studies in animals, but not established or not studied in humans; may use if benefits outweigh risk to fetus.
Precautions	Caution in Down syndrome and/or children with brain damage to prevent hyperreactive response; caution in coronary heart disease, tachycardia, congestive heart failure, cardiac arrhythmias, hypertension, peritonitis, ulcerative colitis, hepatic disease, and hiatal hernia with reflux esophagitis; in prostatic hypertrophy, prostatism can have dysuria and may require catheterization.

2. Drug Category: Corticosteroids

Inhibit arachidonic acid release from phospholipids, inhibit the transcription and action of cytokines, and limit B-cell and T-cell activity. Indicated in inflammatory diseases of a noninfectious cause. Four routes of administration are available: topical, periocular, intraocular, and systemic. The best route and dose is determined for each patient, but the minimum amount needed to control inflammation should be used to reduce complications. Because of serious adverse effects, especially with high doses and long-term use, immunosuppressive agents commonly are used for chronic or sight-threatening uveitis.

Drug Name	***PREDNISOLONE (PRED FORTE)***
Description	Treats acute inflammations following eye surgery or other types of insults to eye. Decreases inflammation and corneal neovascularization. Suppresses migration of polymorphonuclear leukocytes and reverses increased capillary permeability. In cases of bacterial infections, concomitant use of anti-infective agents is mandatory; if signs and symptoms do not improve after 2 days, reevaluate patient. Dosing may be reduced, but the patients should not discontinue therapy prematurely.
Adult Dose	Shake well before using; 1 gtt OU qd or up to q1h while awake.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity; viral, fungal, or tubercular infections.
Interactions	None reported.
Pregnancy	C – Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus.
Precautions	Caution in hypertension; known to cause cataract formation with long-term use; suspect fungal invasion in any persistent corneal ulceration where a corticosteroid has been used or is in use (obtain fungal cultures when appropriate).

Drug Name	*TRIAMCINOLONE (AMCORT, KENALOG, ARISTOCORT)*
Description	Triamcinolone is a synthetic glucocorticoid corticosteroid with marked anti-inflammatory action. Triamcinolone ophthalmic is injected into the eye to treat inflammation caused by disease or injury. Triamcinolone is usually given after steroid eye drops have been used without successful treatment of symptoms.
Adult Dose	20-40 mg sub-Tenon or trans septal injection; may repeat in 2-3 wk. 4mg/0.1ml intravitreal injection; may repeat in 4wk.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity; fungal, viral, and bacterial skin infections.
Interactions	Coadministration with barbiturates, phenytoin, and rifampin decreases effects of triamcinolone.
Pregnancy	C – Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus.
Precautions	Multiple complications (e.g., severe infections, hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression) may occur; abrupt discontinuation of glucocorticoids may cause adrenal crisis.

Drug Name	*PREDNISONE (DELATASONE, ORASONE, METICORTEN, STERAPRED)*
Description	May be used if topical therapy is not adequate to treat iritis (especially in bilateral cases). May decrease inflammation by reversing increased capillary permeability and suppressing PMN activity.
Adult Dose	1 mg/kg/d PO; taper over 3-6 weeks as symptoms resolve.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity; viral infection; peptic ulcer disease; hepatic dysfunction; connective tissue infections; fungal or tubercular skin infections; GI tract disease.
Interactions	Coadministration with estrogens may decrease prednisone clearance; concurrent use with digoxin may cause digitalis toxicity secondary to hypokalemia; Phenobarbital, phenytoin, and rifampin may increase metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics.
Pregnancy	B- Fetal risk not confirmed in studies in humans but has been shown in some studies in animals.
Precautions	Abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur.

3. Drug Category: Immunosuppressive agents

Include 3 main cathegories of therapy: antimetabolites, T-cell suppressors, and cytotoxic agents. Antimetabolites include azathioprine, methotrexate, and mycophenolatemofetil. T-cell inhibitors include cyclosporine and tacrolimus. Cytotoxic agents are alkylating agents that include cyclophosphamide and chlorambucil. Most agents take several weeks to achieve efficacy; therefore, they initially are used in conjunction with oral corticosteroids. Once the disease is under control, corticosteroids can be tapered. Instituting these agents and monitoring of adverse events in conjunction with a specialist who has expertise with these agents is strongly recommended.

Drug Name	***AZATHIOPRINE (IMURAN)***
Description	Nucleoside analog that interferes with DNA replication and RNA transcription. Decreases peripheral T – and B – lymphocyte count, and reduces lymphocyte activity. Metabolism is dependent on xanthine oxidase. May decrease proliferation of immune cells, which results in lower autoimmune activity. Indicates to treat Behçet's disease or chronic uveitis, especially with oral corticosteroids.
Adult Dose	1 mg/kg/d PO initially; not to exceed 2.5-4 mg/kg/d.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity; low levels of serum TPMT.
Interactions	Toxicity increases with allopurinol (decrease dose); concurrent use with ACE inhibitors may induce severe leucopenia; may increase levels of methotrexate metabolites and decrease effects of anticoagulants, neuromuscular blockers, and cyclosporine.
Pregnancy	D –Fetal risk shown in humans; use only if benefits outweigh risk to fetus.
Precautions	Increases risk of neoplasia; caution with liver disease and renal impairment; hematologic toxicities may occur; check TPMT level prior to therapy; monitor liver (check q 12wk), renal, and hematologic (check CBC q4-6wk) function; pancreatitis rarely associated.

Drug Name	*METHOTREXATE (RHEUMATREX, FOLEX PFS)*
Description	Folic acid analog and inhibitor of dihydrofolate n-reductase, which is the enzyme responsible for the conversion of dihydrofolate to tetrahydrofolate. Arrests DNA replication, inhibiting rapidly dividing cells (e.g., leukocytes). Eliminated primarily through the kidney. Used to treat various ocular inflammatory diseases, including vasculitis, panuveitis, intermediate uveitis, and vitritis.
Adult Dose	7.5-12.5 mg/wk PO initially; not to exceed 25 mg/wk; folate (1 mg/d) is given concurrently to minimize nausea.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity; alcoholism; hepatic insufficiency; documented immunodeficiency syndromes; preexisting blood dyscrasias (e.g., bone marrow hypoplasia, leucopenia, thrombocytopenia, significant anemia); renal insufficiency.
Interactions	Oral aminoglycosides may decrease absorption and blood levels of concurrent oral MTX (methotrexate); charcoal lowers MTX levels; coadministration with etretinate may increase hepatotoxity of MTX; folic acid or its derivatives contained in some vitamins may decrease response to MTX; indomethacin and phenylbutazone can increase MTX plasma levels; may decrease phenytoin serum levels; probenecid, salicylates, procarbazine, and sulfonamides, including TMP-SMZ, may increase effects and toxicity of MTX; may increase plasma levels of thiopurines.
Pregnancy	D – Fetal risk shown in humans; use only if benefits outweigh risk to fetus
Precautions	Obtain CBC, CHEM-7, and hepatitis B and C antibodies at initiation of therapy; monitor CBC and liver and renal function q1-2mo during therapy (monitor more frequently during initial dosing, dose adjustments, or when risk of elevated MTX levels, e.g, dehydration); MTX has toxic effects on hematologic, renal, GI, pulmonary, and neurologic systems; patient should try to abstein from alcohol consumption; discontinue if significant drop in blood counts; aspirin, NSAIDs, or low-dose steroids may be administered concomitantly with MTX (possibility of increased toxicity with NSAIDs, including salicylates, has not been tested).

Drug Name	*CHLORAMBUCIL (LEUKERAN)*
Description	Alkylating agent that substitutes an alkyl group for hydrogen ions in organic compounds. DNA-to-DNA intrastrand cross-linking and DNA-to-protein cross-linking occurs, which lead to interference in DNA replication and transcription. Metabolism occurs in liver. Small studies suggest it may be effective for various sight-threatening uveitic syndromes, including Behçet's disease and sympathetic ophthalmia.
Adult Dose	0.1 mg/kg/d PO initially; not to exceed 0.2 mg/kg/d.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity; previous resistance to medication.
Interactions	None reported.
Pregnancy	D – Fetal risk shown in humans; use only if benefits outweigh risk to fetus.
Precautions	Caution in history of seizure disorders or diagnosed with bone marrow suppression; opportunistic infections may occur; monitor CBC q1wk; alkylating agents may increase risk of primary or secondary malignancy.

Drug Name	*CYCLOPHOSPHAMIDE (NEOSAR, CYTOXAN)*
Description	Chemically related to nitrogen mustards. As an alkylating agent, mechanism of action of the active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells. Cytotoxic to resting and dividing lymphocytes. Primarily excreted through kidney.
Adult Dose	2mg/kg/d PO initially; not to exceed 3mg/kg/d.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity; severely depressed bone marrow function.
Interactions	Allopurinol may increase risk of bleeding or infection and enhance myelosuppressive effects; may potentiate doxorubicin-induced cardiotoxicity; may reduce digoxin serum levels and antimicrobial effects of fluoroquinolones; chloramphenicol may increase half-life while decreasing metabolite concentrations; may increase effect of anticoagulants; coadministration with high doses of Phenobarbital may increase rate of metabolism and leukopenic activity; thiazide diuretics may prolong cyclophosphamide-induced leokopenic activity; thiazide diuretics may prolong cyclophosphamide-induced leucopenia, and neuromuscular blokade by inhibiting cholinesterase activity.
Pregnancy	D-Fetal risk shown in humans; use only if benefits outweigh risk to fetus
Precautions	Regularly examine hematologic profile (particularly neutrophils and platelets) to monitor for hematopoietic suppression; regularly examine urine for RBCs, which may precede hemorrhagic cystitis; adverse effects include ovarian suppression, testicular atrophy, alopecia, nausea, and vomiting; initially obtain CBC and urinalysis q1wk; alkylating agents may increase risk of primary or secondary malignancy.

Drug Name	*TACROLIMUS (PROGRAF)*
Description	Macrolide immunosuppressant naturally produced, which suppresses humoral immunity (T lymphocyte) activity. Metabolized by the cytochrome P-450 system. Small, uncontrolled case series suggested that it might be effective for treating noninfectious uveitits.
Adult Dose	0.15-0.3 mg/kg/d PO initially; not to exceed 0.3 mg/kg/d.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity.
Interactions	Levels may increase with diltiazem, nicardipine, clotrimazole, verapamil, erythromycin, ketaconazol, itraconazol, fluconazol, bromocriptine, grapefruit juice, metoclopramide, methilprednisolone, danazol, cyclosporine, cimetidine, and clarithomycin; levels may be reduced with rifabutin, rifampin, Phenobarbital, phenytoin, and carbamazepine.
Pregnancy	C – Fetal risk revealed in studies in animals but not established or not studied in humans; may use it benefits outweigh risk to fetus.
Precautions	Frequently evaluate renal and liver functions by measuring BUN, serum creatinine, serun bilirubin, and liver enzymes; may increase risk of infection and lymphoma; reserve IV use only for those who cannot take PO; renal impairment and neurologic and GI tract symptoms are major adverse effects that resolve with drug discontinuance; LFTs, BUN, creatinine, CHEM-7, CBC, and lipid profiles are recommended q1wk(initially).

Drug Name	*MYCOPHENOLATE, (CELLCEPT)*
Description	Selective inhibitor of inosine monophosphate dehydrogenase, which interferes with guanosine nucleotide synthesis. Prevents lymphocyte proliferation, suppresses antibody synthesis, interferes with cellular adhesion to vascular endothelium, and decreases recruitment of leukocytes to sites of inflammation. Metabolized primarily through the kidneys. Used in combination with other agents, particularly oral corticosteroids. May be an acceptable alternative to azathioprine or methotrexate, especially in patients intolerant of other agents.
Adult Dose	500 mg PO bid initially; not to exceed 1.5 g bid.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity.
Interactions	May elevate levels of acyclovir and ganciclovir; antacids and cholestyramine decrease absorption, reducing levels (do not coadminister); probenecid may increase levels of mycophenolate; salicylates may increase toxicity of mycophenolate.
Pregnancy	D-Fetal risk shown in humans; use only if benefits outweigh risk fetus
Precautions	Increases risk for infection; increases toxicity in patients with renal impairment; caution in active peptic ulcer disease; GI tract problems are common and include pain, nausea, vomiting, and diarrhea; at doses approaching 3g/d for transplant patients, complications of leucopenia, lymphoma, and non-melanoma skin cancers are reported; monitor with CBC q1w and LFTs q3mo.

Drug Name	*CYCLOSPORINE (NEORAL, SANDIMMUNE)*
Description	Inhibitor of transcription in T lymphocytes that are in the G0 and G1 phase of their cell cycle, which blocks replication and ability to produce lymphokines. Metabolized in liver. Useful as sole therapy for various uveitis conditions.
Adult Dose	2.5-5mg/kg/d PO initially; not to exceed 10mg/kg/d.
Pediatric Dose	Not established.
Contraindications	Documented hypersensitivity; uncontrolled hypertension; malignances; do not administer concomitantly with PUPA or UV-B radiation in psoriasis since it may increase risk of cancer.
Interactions	Carbamazepine, phenytoin, isoniazid, rifampin, and phenobarbital may decrease cyclosporine concentrations; azithromycin, itraconazole, nicardipine, ketoconazole, fluconazole, erythromycin, verapamil, grapefruit juice, diltiazem, aminoglycosides, acyclovir, anphotericin B, and clarithomycin may increase cyclosporine toxicity; acute renal failure, rhabdomyolysis, myositis, and myalgias increase taken concurrently with lovastatin.
Pregnancy	C – fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus.
Precautions	Evaluate renal and liver functions often by measuring BUN, serum creatinine (check q2wk), serum bilirubin, and liver enzymes; may increase risk of infection and lymphoma; reserve IV use only for those who cannot take PO; adverse effects include nephrotoxicity, hypertension, hepatotoxity, gingival hyperplasia, myalgias, tremor, and hirsutism; check blood pressure at every visit.

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We are committed to provide you with professional, state-of-the-art medical and surgical care for your eyes. From performing routine eye examinations to complex ocular inflammation and retina surgeries.

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